

Serial No.: 09/981,289

Filed: October 15, 2001

REMARKS

Claims 1-3 and 13-16 are pending in this application. New Claims 17-28 have been added by this Amendment. Claims 1-16 have been amended to clarify the language of the claims. Support for amendments may be found in the Specification at page 2, lines 2-4, and lines 19-24; page 18, line 30; page 19, lines 6-9; page 21 lines 16-31; page 22, lines 1-13; page 24, lines 16-17; page 25, lines 16-33; page 26, lines 1-10; Figure 1B; Figure 5 and Figure 6.

Support for new Claim 17 may be found in the Specification at page 19, lines 23-28 and page 24, lines 16-17. Support for new Claim may be found in the Specification at page 2, lines 19-32; page 6, lines 3-8 and lines 25-30 page 18, line 30; page 19, lines 1-9; page 22, lines 10-13; page 23, lines 3-10; page 25, lines 21-23 page 26, lines 1-10 and original claim 1. Support for new Claim 19 may be found for example, in the Specification at page 2, lines 19-32; page 6, lines 3-8 and lines 25-30; page 18, line 30; page 19, lines 1-9; page 22, lines 10-13; page 25, lines 21-23; and page 26, lines 1-10. Support for new Claim 20 may be found in the Specification at page 2, lines 19-26; page 19, lines 7-10; page 22, lines 10-13; page 25, lines 21-23; and page 26, lines 1-10. Support for new Claim 21 may be found for example, in the Specification at page 22, lines 10-13; page 25, lines 21-23; and page 26, lines 1-10. Support for new Claim 22 may be found in the Specification at page 22, lines 10-13; page 25, lines 21-23; and page 26, lines 1-10. Support for new Claim 23 may be found in the Specification at page 22, lines 10-13; page 25, lines 21-23; and page 26, lines 1-10. Support for new Claim 24 may be found in the Specification at page 22, lines 10-13; page 25, lines 21-23; and page 26, lines 1-10. Support for new Claim 25 may be found in the Specification at page 22, lines 10-13; page 25, lines 21-23 and page 26, lines 1-10. Support for new Claim 26 may be found in the Specification for example at page 48, lines 1-4. Support for new Claim 27 may be found in the Specification at page 2, lines 10-11 and lines 15-19; page 5, lines 26-27 and line 30-32; page 19, lines 6-9 page 22, lines 1-9; and Figure 9; Figures 10A and 10B. Support for new Claim 28 may be found in the Specification at page 2, lines 21-26, page 22, lines 1-5; page 28, lines 20-21 and Figure 7.

Applicants respectfully submit that no new matter has been added by the amendments to the claims. Additionally, Applications confirm that inventorship has not been changed by the amendments to the claims.

Claim Rejection under 35 USC §112, first paragraph

Claims 1-3 and 13-16 have been rejected under 35 USC §112, first paragraph as containing subject matter which was not described in the specification in a way to reasonably convey to one skilled in the art that Applicants had possession of the claimed invention at the time the application was filed.

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Applicants respectfully submit that the Office Action at page 2, paragraph 6, states that the Declaration submitted by Dr. Robert Hayes, removed the 112, first paragraph rejection.

Claim Rejection under 35 USC §102

Claims 1, 2, 14, 15, and 16 have been rejected under 35 USC §102(b) as being anticipated by Banner et al. (U.S. Pat No. 5, 597,899). The Examiner states that the mutations made by Banner have the inherent feature of forming mixed trimers, thus anticipating Claims 1, 2, 14, 15, and 16. Applicants disagree for the following reasons.

Banner teaches the production of mutations at several different amino acid positions compared to wild type TNF- α , which has different binding affinity to p55-TNFR as compared to p75-TNFR. However, as the Examiner notes, Banner does not teach the formation of mixed trimer formation due to the presence of variant TNF- α .

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)."

The Examiner has mischaracterized Banner, which does not suggest, teach or disclose the formation of mixed trimers. In contrast, the present invention teaches and claims mixed trimers. Banner et al., does not teach trimers, nor is there any suggestion of trimers or trimerization. Banner et al. do not suggest, teach or disclose the concept of mixed trimers, that is, 1:2 or 2:1 combinations of naturally occurring human TNF- α with the variants of the present invention. See Figure 1B which shows a depiction of one embodiment of a mixed trimer complex that inactivates receptor signaling. Nor is the concept of a trimer of variants suggested or taught. The mere fact that some of the substitutions of Banner et al. overlap with Applicants variants, does not necessarily mean that the Banner et al. variants could form trimers, exchange with naturally occurring human TNF- α and/or inactivate receptor signaling, because it is not necessarily an inherent property of all possible TNF- α variants and perhaps Banner et al.'s variants. It is possible that by modifying TNF- α , trimerization could be blocked. Applicant's variants were designed to specifically trimerize. See specification at page 4, lines 1 and 2 and Figure 8, which shows variant TNF- α agonists, which would prevent not receptor signaling and are specifically outside the scope of Applicant's claims.

Additionally, the trimers are incapable of activating receptor signaling. The present invention is directed to modified TNF- α monomers, which exchange or interact (e.g., trimerize) with naturally occurring human TNF- α in vivo, thus sequestering naturally occurring human TNF- α into a complex

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incapable of signaling. See for example, Specification at page 2, lines 19-26 and page 23, lines 3-12 and Figure 1B. On the other hand, Banner et al. teach enhanced receptor binding specificity, that is, Banner et al. find binding to a particular receptor and activating the specific receptor signaling advantageous. Applicants specifically do not want to activate receptor signaling and the claims recite this limitation.

As can be seen from the above discussion, Banner et al. do not suggest, teach or disclose exchange between variants and/or naturally occurring human TNF-a to form mixed trimers, and teaches away from receptor activation. Therefore, Banner et al. do not teach each and every element of the invention as claimed, the cited reference does not anticipate the invention. In light of the foregoing arguments, Applicants respectfully request the reconsideration and withdrawal of the claim rejections.

Claim Rejection under 35 USC §112, second paragraph.

Claims 1-3 and 13-16 are rejected as vague and indefinite for reciting the term "non-naturally occurring". Applicants submit that the term is defined in the specification at page 25, lines 20-23. With respect to Examiner's comments regarding the determination of the source of the variants, Applicants have clarified the claims to reflect the fact that the non-naturally occurring variants are compared to naturally occurring human TNF-a.

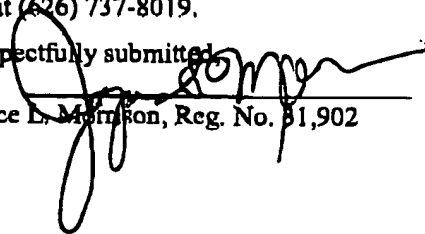
The Examiner also rejects claims 3, 14 and 15 "for providing the species information of the TNF-a protein". Applicant's interpret this rejection to mean that Examiner is requiring a specific recitation in the claims of the species of origin. As discussed above, Applicant's have added the term "human" to the naturally occurring TNF-a to clarify the species as well as the position numbering.

Claim 16 is rejected for omitting essential steps regarding recovery. Applicants have modified this claim and believe that this rejection is now moot.

Applicants thank the Examiner for noting that positions 21, 30, 31, 32, 35, 66, 111, 112, 140, and substitutions K112D, Y115T, D143K, D143R, and Y115I are free from prior art.

The Applicants submit that in light of the above-amendment and argument, the claims are now in condition for allowance and an early notification of such is respectfully solicited. Please direct any calls in connection with this application to the undersigned at (626) 737-8019.

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Respectfully submitted,
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